WHAT IS CLAIMED IS:

1. An *in vivo* method of affinity maturation by competitive activation to obtain a binding molecule that has an enhanced affinity for a target binding ensemble member relative to that of a reference binding molecule, the method comprising:

(a) recombinantly altering a population of host cells by

(i) introducing into the host cells a library of genes encoding candidate binding molecules;

(ii) introducing into the host cells a competitive activation system comprising a nucleic acid encoding a responder molecule linked to the target binding ensemble member, and a nucleic acid encoding a competitor binding molecule linked to an inhibitor of the responder complex;

(b) incubating the host cells under conditions in which the library and competitive activation system are expressed and where the responder molecule is activated when a candidate binding molecule binds to the target binding ensemble member; and

(c) detecting cells having a signal from the responder molecule that corresponds to a candidate binding molecule binding affinity for the target binding ensemble member that is greater than that of the reference binding molecule, thereby identifying a candidate binding molecule with an enhanced affinity for the target binding ensemble member.

2. The method of claim 1, wherein the reference binding molecule is a reference antibody and the target binding ensemble member is an antigen to which the reference antibody specifically binds.

3. The method of claim 2, further wherein the competitor binding molecule is the reference antibody.

4. The method of claim 3, wherein the reference antibody is an Fab fragment.

5. The method of claim 3, wherein the reference antibody is a single chain Fv.

6. The method of claim 2, further wherein the candidate binding molecules are single chain Fvs.

7. The method of claim 2, further wherein the candidate binding molecules are Fab fragments.

8. The method of claim 2, further wherein the candidate binding molecules are single V-region domains.

9. The method of claim 1, wherein the candidate binding molecules are scaffolded peptides.

10. The method of claim 1, wherein the candidate binding molecules are mutagenized natural ligands of the target binding ensemble member.

11. The method of claim 2, further wherein the library of candidate binding molecules comprises hybrid antibodies that have at least one CDR in a V_H or V_L that is different from the reference antibody and is from a natural antibody repertoire.

12. The method of claim 11, wherein the hybrid antibodies have either a V_H or V_L from the reference antibody and the corresponding V_H or V_L from a natural antibody repertoire.

13. The method of claim 2, further wherein the competitor binding molecule is a nonhuman antibody and the candidate binding molecules are antibodies having at least one human variable region.

14. The method of claim 2, further wherein the competitor binding molecule is a natural ligand of the antigen that competes with the reference antibody for binding to the antigen.

15. The method of claim 2, wherein the competitor binding molecule is an artificial non-antibody ligand of the antigen that competes with the reference antibody for binding to the antigen.

16. The method of claim 1, wherein the responder molecule is an enzyme.

17. An *in vivo* method of affinity maturation by competitive activation to obtain a binding molecule that has an enhanced affinity for a target binding ensemble member relative to that of a reference binding molecule, the method comprising:

(a) recombinantly altering a population of host cells by

(i) introducing into the host cells a library of genes encoding candidate binding molecules;

(ii) introducing into the host cells a competitive activation system comprising a nucleic acid encoding a responder molecule linked to a competitor binding molecule, and a nucleic acid encoding an inhibitor linked to the target binding ensemble member;

(b) incubating the host cells under conditions in which the library and competitive activation system are expressed and where the responder molecule is activated when a candidate binding molecule binds to the target binding ensemble member; and

(c) detecting cells having a signal from the responder molecule that corresponds to a candidate binding molecule affinity for the target ensemble member that is greater than that of the reference binding molecule, thereby identifying a candidate binding molecule with an enhanced affinity for the target binding ensemble member.

18. The method of claim 17, wherein the reference binding molecule is a reference antibody and the target binding ensemble member is an antigen to which the reference antibody specifically binds.

19. The method of claim 18, further wherein the competitor binding molecule is the reference antibody.

20. The method of claim 19, wherein the reference antibody is an Fab fragment.

21. The method of claim 19, wherein the reference antibody is a single chain Fv.

22. The method of claim 18, further wherein the candidate binding molecules are single chain Fvs.

23. The method of claim 18, further wherein the candidate binding molecules are Fab fragments.

24. The method of claim 18, further wherein the candidate binding molecules are single V-region domains.

25. The method of claim 17, further wherein the candidate binding molecules are scaffolded peptides.

26. The method of claim 17, further wherein the candidate binding molecules are mutagenized natural ligands of the target binding ensemble member.

27. The method of claim 18, further wherein the library of candidate binding molecules comprises hybrid antibodies that have at least one CDR in a V_H or V_L that is different from the reference antibody and is from a natural antibody repertoire.

28. The method of claim 27, wherein the hybrid antibodies have either a V_H or V_L from the reference antibody and the corresponding V_H or V_L from a natural antibody repertoire.

29. The method of claim 18, further wherein the competitor binding molecule is a nonhuman antibody and the candidate binding molecules are antibodies having at least one human variable region.

30. The method of claim 18, further wherein the competitor binding molecule is an artificial non antibody ligand of the antigen that competes with the reference antibody for binding to the antigen.

31. The method of claim 18, wherein the competitor binding molecule is an artificial non-antibody ligand of the target antigen that competes with the reference antibody for binding to the target antigen.

32. The method of claim 18, wherein the responder molecule is an enzyme.

33. An *in vivo* method of affinity maturation by auto-inhibited reactivation to obtain a binding molecule that has an enhanced affinity for a target binding ensemble member relative to a reference binding molecule, the method comprising:

(a) recombinantly altering a population of host cells by

(i) introducing into the host cells a competitor that binds to the target binding ensemble member with the same specificity as a reference binding molecule;

(ii) introducing into the host cells a nucleic acid encoding a reactivator complex comprising a reactivator molecule linked to the target binding ensemble member;

(iii) introducing into the host cells a library of genes, each of which encodes an auto-inhibited responder complex comprising a responder molecule linked to an inhibitor and linked to a candidate binding molecule;

(b) incubating the host cells under conditions in which the competitor, the reactivator complex, and the auto-inhibited responder library are expressed where the responder molecule is activated when a candidate binding molecule binds to the target binding ensemble member; and

(c) detecting cells having a signal from the responder molecule that corresponds to a candidate binding molecule affinity for the target binding ensemble member that is greater than that of the reference binding molecule, thereby identifying a candidate binding molecule with an enhanced affinity for the target binding ensemble member.

34. The method of claim 33, wherein the reference binding molecule is an antibody and the target binding ensemble member is an antigen to which the reference antibody specifically binds.

35. The method of claim 34, further wherein the competitor is the reference antibody.

36. The method of claim 35, further wherein the reference antibody is an Fab fragment.

37. The method of claim 35, further wherein the reference antibody is a single chain Fv (scFv).

38. The method of claim 34, further wherein the candidate binding molecules are single chain Fvs.

39. The method of claim 34, further wherein the candidate binding molecules are Fab fragments.

40. The method of claim 34, further wherein the candidate binding molecules are single V-region domains.

41. The method of claim 33, wherein the candidate binding molecules are scaffolded peptides.

42. The method of claim 33, wherein the candidate binding molecules are mutagenized ligands.

43. The method of claim 34, further wherein the candidate binding molecules are hybrid antibodies that have at least one CDR in a V_H or V_L that is different from the reference antibody and is from a natural antibody repertoire.

44. The method of claim 43, wherein the hybrid antibodies have either a V_H or V_L from the reference antibody and the corresponding V_H or V_L from a natural antibody repertoire.

45. The method of claim 34, further wherein the competitor is a nonhuman antibody and the candidate binding molecules comprise antibodies having at least one human variable region.

46. The method of claim 34, further wherein the competitor is a scaffolded peptide that competes with the reference antibody for binding to the antigen.

47. The method of claim 34, further wherein the competitor is an artificial non-antibody ligand of the antigen that competes with the reference antibody for binding to the antigen.

48. A method of affinity maturation by self-inhibited reactivation to obtain a binding molecule that has a higher affinity for a target binding ensemble member than that of a reference binding molecule, the method comprising:

(a) recombinantly altering a population of host cells by

(i) introducing into the host cells a competitor binding molecule that binds to a target binding ensemble member with the same specificity as the reference binding molecule,

(ii) introducing into the host cells a nucleic acid encoding an auto-inhibited responder complex comprising a responder molecule linked to an inhibitor and to the target binding ensemble member,

(iii) introducing into the host cells a library of genes, each encoding a reactivator complex, wherein each gene encodes a reactivator molecule linked to a candidate binding molecule;

(b) incubating the host cells under conditions in which the competitor, the auto-inhibited responder-target binding ensemble member complex, and the reactivator library complex are expressed and where the responder molecule is activated when a candidate binding molecule binds to the target binding ensemble member; and

(c) detecting cells having a signal from the responder molecule that corresponds to a candidate binding molecule affinity for the target binding ensemble member that is greater than that of the reference binding molecule, thereby identifying a candidate binding molecule with an enhanced affinity for the target binding ensemble member.

49. The method of claim 47, wherein the reference binding molecule is a reference antibody and the target binding ensemble member is an antigen to which the reference antibody specifically binds.

50. The method of claim 49, further wherein the competitor is the reference antibody.

51. The method of claim 49, wherein the reference antibody is an Fab fragment.

52. The method of claim 49, wherein the reference antibody is a single chain Fv (scFv).

53. The method of claim 49, further wherein the candidate binding molecules are single chain Fvs.

54. The method of claim 49, wherein the candidate binding molecules are Fab fragments.

55. The method of claim 49, wherein the candidate binding molecules are single V-region domains.

56. The method of claim 47, wherein the candidate binding molecules are scaffolded peptides.

57. The method of claim 47, wherein the candidate binding molecules are mutagenized natural ligands that specifically bind the target binding ensemble member.

58. The method of claim 49, further wherein the candidate binding molecules are hybrid antibodies that have at least one CDR in a V_H or V_L that is different from the reference antibody and is from a natural antibody repertoire.

59. The method of claim 58, wherein the hybrid antibodies have either a V_H or V_L from the reference antibody and the corresponding V_H or V_L from a natural antibody repertoire.

60. The method of claim 49, further wherein the reference antibody is a nonhuman antibody and the candidate binding molecules are antibodies having at least one human variable region.

61. The method of claim 49, further wherein the competitor is a natural ligand of the target antigen that competes with the reference antibody for binding to the antigen.

62. The method of claim 49, wherein the competitor is a natural ligand of the antigen that competes with the reference antibody for binding to the antigen.